in the knowledge generally available among those of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success found in the prior art. Third, the prior art reference must teach or suggest all the claim limitations. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

No Reference Alone, Nor Any Combination Thereof, Teaches or Suggests All Of The Features Of Any Of The Claims.

The Office Action has cited two primary references that allegedly can be combined with various secondary references to render obvious the claimed invention. However, the Office Action has not established a *prima facie* case of obviousness, because the cited references, even if they were properly combinable, do not disclose or suggest all of the features of the invention to which Claim 1 is directed.

Claim 1 recites:

A method of inducing and/or sustaining an immunological CTL response in a mammal, which method comprises:

delivering an antigen to the mammal at a level sufficient to induce an immunologic CTL response in the mammal; and

maintaining the antigen in the mammal's lymphatic system over time sufficient to maintain the immunologic CTL response.

None of the cited references reports achieving an immunologic CTL response that is maintained. Maintaining the antigen in the mammal's lymphatic system over time sufficient to maintain the immunologic CTL response provides for potent and sustained CTL stimulation that is necessary to keep CTLs active, cytotoxic and recirculating throughout the body. The references do not indicate maintenance of this kind of response. Since none of the cited references discloses this feature of the independent claim, the PTO has not borne its burden of establishing a *prima facie* case of obviousness, even if it were proper to combine some or all of the cited references.

Since all of the pending claims incorporate this feature, it follows that there is no *prima facie* case of obviousness established for any of the claims, and Applicants respectfully request that the rejections listed in the Office Action be withdrawn.

Applicants have selected this particular claim feature as one clear deficiency in the cited prior art. However, this focused argument is not intended to indicate that this is the only basis on which Applicants could distinguish the claims over the prior art, and Applicants reserve the right to do so later, if necessary.

Neither Grohmann et al. ("Grohmann") nor Puccetti et al. ("Puccetti"), alone or in combination, teaches induction and maintenance of an immunologic CTL response. In fact, both illustrate the lack of understanding and appreciation of the technology of the present invention at the time they were published (Grohmann 1991, Puccetti 1994). There is no disclosure in either reference indicating induction and maintenance of T cell function beyond T cell memory. *See* Grohmann at 9 and 13; Puccetti at 1446, 1450-51.

Grohmann discloses the surgical implantation of an antigen bound to a membrane strip in order to elicit a humoral and a cellular immune response. *See* Grohmann at 10. Grohmann reports both a $CD8^+$ T cell-mediated DTH response and increased CTLp (CTL precursors), neither of which demonstrates existent CTL activity in the subject animal. (Generally, DTH is mediated by T cells, and is characterized by inflammation, induration, swelling and monocytic infiltration into the secondary site of antigen exposure within 24 to 72 hours. A CTLp assay involves an *in vitro* secondary stimulation to reactivate quiescent cells. Thus, neither indicates a maintained immunologic CTL response.) Lytic activity demonstrable directly in explanted cells (*i.e.* without an *in vitro* secondary stimulation) is one way to demonstrate maintenance of antigen, whereas detection of CTLp or DTH is not. *See* specification at Example 3, page 63. Since Grohmann discloses only CTLp and DTH data, and is silent as to primary lytic activity, Grohmann fails to show any maintained immunologic CTL response as set forth in Claim 1. Further, since detection of a maintained immunologic CTL response is a surrogate for demonstrating maintenance of the antigen in the mammal's lymphatic system over time, Grohmann's failure to show a maintained immunologic CTL response is likewise a failure to show actual maintenance of the antigen in the lymphatic system over time.

Likewise, Puccetti fails to disclose maintenance of an immunologic CTL response. Puccetti discloses a possible test for detecting a $CD8^+$ T cell-mediated DTH response *in vivo* and uses this test to assess various immunization protocols. *See* Puccetti at 1446. In one experiment mice had peptide antigen bound to membrane strips surgically implanted into their spleens. *See id* at 1447. Later, the mice were challenged subcutaneously with antigen, and measurements were taken of footpad thickness and weight in order to assess DTH. *See id.* As discussed above, the alleged DTH response does not demonstrate or imply an immunologic CTL response. Moreover, Puccetti provides no discussion or teaching on how to maintain antigen in order to maintain an immunologic CTL response, or on the desirability of doing so. In fact, Puccetti explicitly points out that the immunizing peptide has a presumably short half life, but that evidence indicates that persistence of antigen is not required to maintain T cell memory. *See id* at 1540. Therefore, Puccetti fails to provide any disclosure of inducing and/or maintaining an immunologic CTL response as recited in Claim 1.

None of the secondary references adds the particular feature of maintaining the antigen in the mammal's lymphatic system over time sufficient to maintain the immunologic CTL response. Mertelsmann et al. ("Mertelsmann") (U.S. Patent No. 4, 908,433) discloses uses of interleukin-2. Nabel et al. ("Nabel") (U.S. Patent No. 5,328, 470) is directed to disease treatment by site-specific delivery of proteins and genes. Amkraut et al. ("Amkraut") (U.S. Patent No. 4,439,199) discloses a method for administering immunopotentiators to activate an immune response as quantified, for example, by antibody assays. Finally, Elliott et al. ("Elliott") (U.S. Patent No. 5,478,556) discloses a particular breast cancer vaccine and composition. None of these references provides disclosure of maintaining an antigen in the mammal's lymphatic system over time sufficient to maintain an immunologic CTL response as disclosed in Claim 1.

Claims 43-60 were rejected as being obvious as allegedly reciting well known forms of CTL--inducing antigens, without mention of any specific reference. However, without conceding this assertion by the PTO as to the state of the art, and in view of the lack of a *prima facie* case as to Claim 1, whose features claims 43-60 incorporate, Applicants respectfully request withdrawal of this rejection.

Claim 42 was not explicitly rejected in the Office Action, although it was listed among the rejected claims in the Office Action Summary. In light of the arguments made herein as to the patentability of Claim 1, Applicants submit that Claim 42 is likewise patentable, as it incorporates all of the features of Claim 1.

In light of the above remarks, reconsideration and withdrawal of the outstanding rejections is specifically requested. If the Examiner finds any remaining impediment to the prompt allowance of these claims that could be clarified with a telephone conference, Applicants would welcome a call to their lead attorney, Dale C. Hunt, at the telephone number listed below.

Respectfully submitted,

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Dated: 8/24/01

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